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TITLE: Development of a Personalized Model for Pressure Ulcer Prevention Acutely Following Spinal Cord Injury: Biomarkers of Muscle Composition and Resilience

PRINCIPAL INVESTIGATOR: Katherine Bogie, D.Phil

CONTRACTING ORGANIZATION:
Cleveland VA Medical Research & Education Foundation
Cleveland OH 44106-1702

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14. ABSTRACT Development of a pressure ulcer acutely following spinal cord injury (SCI) has a devastating impact on the progress of initial rehabilitation for too many active duty military and veterans. All persons with SCI are at increased risk of pressure ulcer development which remains one of the most significant secondary complications for these individuals. Susceptibility appears to be unique for each individual. Changes in soft tissue composition and function following SCI may provide the key to personalized risk status which the clinician can employ to determine each individual's optimal pressure ulcer prevention regime. Good risk assessment tools are currently not available to reliably identify the individual with acute SCI at risk of pressure ulcers. This project is investigating potential linkages between skeletal muscle tissue biomarkers and tissue resilience under applied loads in individuals with acute SCI at risk for pressure ulcer development. In the first six months of this observational study we have developed a framework for an objective pressure ulcer risk assessment tool to reliably identify more susceptible individuals within this high-risk population and provide the basis for personalized clinical management of tissue health. Recruitment and data collection are ongoing to collate patient data on tissue health and muscle composition.					
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1. Introduction

Development of a pressure ulcer during the acute phase following injury has a devastating impact on the progress of initial rehabilitation for too many active duty military and veterans with spinal cord injury. All persons with SCI are at increased risk of pressure ulcer development which remains one of the most significant secondary complications for these individuals. Susceptibility appears to be unique for each individual. Changes in soft tissue composition and function following spinal cord injury may provide the key to personalized risk status which the clinician can employ to determine each individual's optimal pressure ulcer prevention regime. Good risk assessment tools are currently not available to reliably identify the individual with acute spinal cord injury at risk of pressure ulcers. This project will investigate potential linkages between skeletal muscle tissue biomarkers and tissue resilience under applied loads in individuals with acute spinal cord injury at risk for pressure ulcer development. This observational study will develop an objective pressure ulcer risk assessment tool to enable clinicians to reliably identify more susceptible individuals within this high-risk population and provide the basis for personalized clinical management of tissue health.

2. Keywords

Spinal cord injury, pressure ulcer prevention, biomarkers, personalized healthcare

3. Accomplishments

Major Project Goals

Task 1: Subject Recruitment and Data Collection: Activity dates: months 1-36,
Percentage completion: 22%

Task 2: Assay and analysis of muscle composition biomarkers: Activity dates: months 1-36
Percentage completion: 22%

Task 3: Development of pressure ulcer risk predictive model: Activity dates: months 1-36
Percentage completion: 20%

Task 4: Data Analyses and Report Writing Activity dates: months 6-36,
Percentage completion: 22%

Accomplishments under these goals

Task 1: Subject Recruitment and Data Collection: Activity dates: months 1-36,

1) Major activities:

a) *Local Institutional Review Board (IRB) and DoD Human Research Protection Office (HRPO) approvals*

All regulatory approvals have been received and are current. *Approved as of 09/30/16*

b-d) *Subject Recruitment and Data Collection*

Sixteen potential participants were screened – three transferred out of the area before recruitment could be completed, four declined to participate, and four had pre-existing DM and were ineligible at the time of screening.

Baseline CT/muscle biopsy & tissue health assessments have been completed for 8 participants.

Annual follow-up CT/muscle biopsy & tissue health assessments have been completed for two participants.

Tissue health questionnaires are being administered weekly (see Task 3c)

In progress

2) Specific objectives

Forty individuals with complete or incomplete SCI within 6 months of injury will be recruited: Recruitment will be stratified to achieve a study cohort that includes participants with and without a history of acute PU. Exclusion criteria will include having an open pelvic region pressure ulcer at the time of recruitment and/or known sensitivity to contrast.

We have found that a large number of the target population have pre-existing diabetes which had initially been an exclusion criteria. In discussion with our clinical team members, it has been determined that individuals with controlled diabetes are essentially the same as those without diabetes. A study modification to revise the exclusion criteria to specify only those with poorly controlled diabetes has been approved and has enabled us to recruit more participants who were previously ineligible.

Pelvic region CT scans with contrast will be carried out following the standardized protocol developed in our previous work. Contrast-free CT scans of the glutei for individuals with high (greater than 75%) or low (less than 10%) intramuscular fat in each sub-group will also be obtained. Gluteal region tissue health will be monitored using our established protocol, specifically tissue oxygenation and blood flow will be monitored using transcutaneous oxygenation and laser Doppler blood techniques. Muscle perfusion will be monitored using near-infra red spectroscopy (NIRS). Tissue health assessments will be carried out in unloaded and supine postures at recruitment. CT scanning and tissue health assessment in unloaded and sitting postures will be obtained once the individual is fully remobilized, and will be repeated annually during the course of the study.

Co-I Dr. Nanette Alvarado routinely collects bone biopsies during clinical diagnostic studies without stopping medications and has found there is no greater risk of bleeding following the procedure. These biopsies are of greater diameter than those carried out in our study, using an 11g needle rather than an 18g. In Dr. Alvarado's expert clinic opinion, it will be safe to carry out muscle biopsies without stopping medications pre-procedure and with the same post-procedural protocol as we already follow, i.e. 20 minutes quiet rest and observation. We therefore submitted and gained approval to expand recruitment eligibility to individuals taking medication that may impact bleeding rates and enable participants to continue their usual medication throughout the duration of their participation in our study.

3) Significant results

Nothing to Report

- 4) Other achievements
Nothing to Report

Task 2: Assay and analysis of muscle composition biomarkers: Activity dates: months 1-36

1) Major activities:

- a) *Development of Case Report Forms for collection of deidentified muscle composition data*

Electronic versions of CRF for muscle composition data collection have been constructed and reviewed by the study team, in particular Dr Alvarado (radiologist) and Dr Sun (biostatistician). The electronic CRF has limited allowed fields for data entry which will prevent errors in study data collection to provide a reliable data source for preliminary model development.
Completed 01/27/15

- b) *Obtain baseline muscle biopsy tissue and plasma from study participants*

Baseline muscle tissue biopsy and blood collections have been completed for eight study participants.
In progress

2) Specific objectives

Circulatory biomarkers associated with muscle composition will be assessed using plasma collected from study participants. Biomarkers involved in fatty metabolism will be assessed at gene and protein levels using quantitative RT-PCR (qRT-PCR) and Western blotting respectively. Local muscle biopsy tissue will be evaluated using the same techniques together with immunohistochemistry to determine localized biomarkers.

3) Significant results

We have some preliminary data showing that the levels of circulatory biomarkers of interest vary in persons with high levels of intramuscular fat (IMAT) compared to those with low IMAT. Specifically fatty acid binding protein 3 (FABP3 - expressed in muscle) and fatty acid binding protein 4 (FABP4 – expressed in adipocytes) were observed in circulatory biomarkers for persons with >20% IMAT (see **Figure 1**) and was not detected in an individual with IMAT less than 10%.

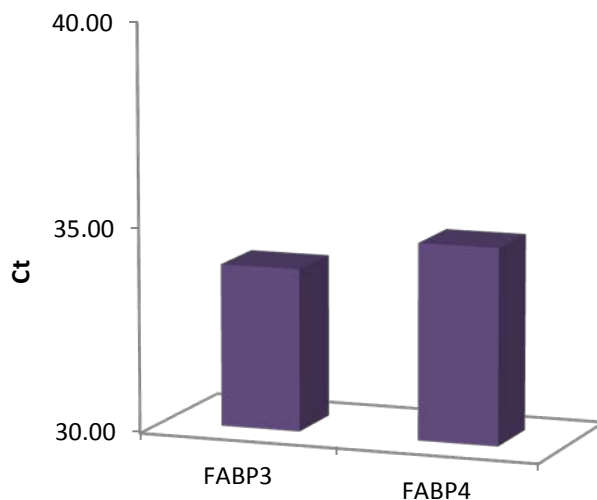


Figure 1: Circulatory Biomarkers in individual with acute SCI and high IMAT.

IMAT =24%
Positive pressure ulcer history

In our testing of circulatory biomarkers of interest we are also investigating the relative levels of biomarkers of interest in whole blood and plasma for study participants. We have found that whole blood gives much higher yields of RNA than plasma. This finding is valuable because it lays the foundation for development of a blood test for PU/DTI risk that can be administered by the individual at home without the need to process blood samples and extract plasma prior to analysis.

- 4) Other achievements
Nothing to Report

Task 3: Development of pressure ulcer risk predictive model: Activity dates: months 1-36

1) Major activities:

a) *Development of Case Report Forms for deidentified data collection.*

Electronic versions of CRF for study participant intake and tissue health data collection were constructed and reviewed by the study team, including Dr Richmond (SCI physician), Dr McDaniel (health scientist) and Dr Sun (biostatistician). The electronic CRF has limited allowed fields for data entry which will prevent errors in study data collection to provide a reliable data source for preliminary model development. *Completed 01/27/15*

b) *Define model structure and implement preliminary model*

The data collected in the CRF will inform the model structure. Consistent data entry will be important so that all data can be analyzed directly from the electronic database. The basic structure of the model has been defined based on the CRF developed on 2(a) and 3(a).

In progress

c) *Study participant follow-up: Short questionnaire format data will be collected from enrolled patients weekly.*

We have developed a 9 item questionnaire which is available via Google docs (<http://goo.gl/forms/fy0QRZ2QKK>) for participants to check in weekly online once discharged. We also contact participants by phone every week because some do not like to use the Internet. *In progress*

2) Specific objectives

A multivariate model of pressure ulcer risk based on muscle composition will be developed based on the tissue health variables and biomarkers assessed under Tasks 1 and 2. Study participants will be followed weekly following recruitment and assessment to determine tissue health status. Incidences of tissue compromise or breakdown will be monitored and data applied to refine the risk model.

- 3) Significant results
Nothing to Report
- 4) Other achievements
Nothing to Report

Task 4: Data Analyses and Report Writing Activity dates: months 6-36,

1) Major activities:

a) Preliminary analysis and initial manuscripts.

In progress

2) Specific objectives

Analysis of project data will validate the original study hypotheses and provide the basis for reliable PU risk assessment acutely following SCI. A predictive model based on muscle composition biomarkers and tissue health assessment will be developed to facilitate personalized PU prevention programs, including pressure relief regimes and selection of support surfaces, to optimize tissue health during initial rehabilitation. Study findings will be presented at local and national meetings and published in the peer-reviewed literature.

3) Significant results

Nothing to Report

4) Other achievements

Nothing to Report

Discussion of stated goals not met

Recruitment continues to be slower than desired. Unfortunately, many Veterans admitted to our facility following SCI are not transferred to LSCDVAMC until they are several months post-injury or are not medically stable until more than 6 months post-injury. They also often already have tissue breakdown on admission. We have therefore submitted a modification to extend inclusion to up to one year post-injury.

We would like to note that at our most recent team meeting, three eligible candidates for the study were identified however enrollment was not complete at the time of this report.

Opportunities for training and professional development

Nothing to Report

Dissemination to communities of interest

We have conducted outreach activities to inform members of our local communities about the study we are conducting. These activities have included outreach to Veterans and non-veterans with spinal cord injury, and professionals involved in the care of individuals with SCI. Goals and early findings have also been presented at national and international professional meetings.

Outreach activities are listed below:

Cleveland VA Research Week May 20th, 2015

Study personnel presented a poster to let Veterans know about our study.

35th Annual National Veterans Wheelchair Games, Dallas, TX June 21-26, 2015

Study coordinator, Ms. Graebert attended the games as a volunteer and spoke to many Veterans both within the Ohio region and nationally about our study.

MetroHealth Rehabilitation Institute of Ohio 20th Annual SCI Forum Sept 11th, 2015

The study team attended the Forum and spoke to many individuals with SCI and clinicians about our study.

Northeast Ohio National Spinal Cord Injury Association (NEONSCIA), Cleveland Ohio
February 15th, 2016

We were also contacted by the local National Spinal Cord Injury Association director who invited us to talk to his group. Dr. Bogie presented an interactive overview of the study and spoke to several NEONSCIA members who were interested in participating in the study.

Oral presentation at Association of Academic Physiatrists (AAP) 2016 Annual Meeting, Sacramento, CA, Feb 16-20, 2016

Personalized pressure ulcer prevention in spinal cord injury: developing a multivariate biomarker approach

KM Bogie, J McDaniel MK Henzel, N Alvarado, M Richmond, J Graebert, T Theofilos

36th Annual National Veterans Wheelchair Games, Salt Lake City, UT June 26- July 1, 2016
Study coordinator, Ms. Graebert attended the games as a volunteer and spoke to many Veterans both within the Ohio region and nationally about our study.

Oral presentation at World Union of Wound Healing Societies (WUWHS) 2016 Quadrennial Congress, Florence, Italy Sept 25-29, 2016

Multivariate biomarkers for personalized pressure ulcer prevention in spinal cord injury

KM Bogie, J McDaniel, MK Henzel, N Alvarado, M Richmond, J Graebert, T Theofilos

In addition to these external outreach meetings we have presented information on our study to inform clinicians at LSCDVAMC about our study at interactive lunch-and-learn sessions with SCI/D physicians, therapists, outpatient service and long-term care nursing personnel.

Plans for next reporting period to accomplish project goals

Task 1: Subject Recruitment and Data Collection:

- Continue recruitment of patients admitted to the SCI/D unit of the LSCDVAMC with acute spinal cord injury with an expansion of the inclusion criteria to include individuals with acute spinal cord injury of less than one year duration
- Expand outreach efforts to Veterans who have already been discharged and non-Veterans at other local facilities in the Cleveland Metro region.
- Continue to obtain baseline pelvic CT scans with contrast following our established protocol.
- Continue to obtain baseline tissue health assessments.
- Continue to obtain follow-up pelvic CT scans with contrast following our established protocol.
- Continue to obtain follow-up tissue health assessments.

Task 2: Assay and analysis of muscle composition biomarkers:

- Continue to obtain baseline muscle biopsy tissue, whole blood and plasma from study participants.
- Continue to obtain follow-up muscle biopsy tissue, whole blood and plasma from study participants.

- Assay muscle tissue whole blood and plasma using quantitative rt-PCR and Western blotting.
- Assay baseline muscle tissue samples using immunohistochemical staining.

Task 3: Development of pressure ulcer risk predictive model:

- Continue to develop and test electronic database based on CRF data collection structure to provide reliable data source for preliminary model.
- Continue weekly collection of skin status using short form questionnaire

Task 4: Data Analyses and Report Writing:

- Submit initial manuscript for publication

4. Impact

Impact on the development of the principal discipline(s) of the project

Nothing to Report

Impact on other disciplines

Nothing to Report

Impact on technology transfer

Nothing to Report

Impact on society beyond science and technology

Nothing to Report

5. Changes/Problems

Changes in approach and reasons for change

In order to accomplish project recruitment goals, the recruitment criteria have been expanded to include individuals with controlled diabetes and those at up to one year post-injury. In addition to individuals taking medication that may impact bleeding rates are now eligible to participate and participants can to continue their usual medication throughout the duration of their participation in our study. These changes enable recruitment of a more comprehensive and representative population of individuals with acute SCI with no increased participant risk. All modifications have been reviewed and approved by the LSCVAMC and HRPO.

Actual or anticipated problems or delays and actions or plans to resolve them

Please see above – due to continued slow recruitment, we have modified the inclusion criteria to encompass a more comprehensive and representative population of individuals with acute SCI. While this will enlarge the pool of potential participants it will not otherwise change the study procedures in any way.

Changes that had a significant impact on expenditures

The changes outlined above have been in progress during the report period. Expenditure has been reduced due to the ongoing slow recruitment.

Significant changes in use or care of human subjects

Nothing to Report

6. Products

Nothing to report

7. Participants & Other Collaborating Organizations

Individuals who have worked on the project

Name: Kath Bogie
Project Role: PI
Researcher Identifier: 0000-0003-1020-9695(ORCID ID)
Nearest person month worked: 2
Contribution to Project: No change

Name: John McDaniel
Project Role: Co-Investigator
Researcher Identifier: N/A
Nearest person month worked: 1
Contribution to Project: Data collection and interpretation

Name: Jennifer Graebert
Project Role: Study Coordinator
Researcher Identifier: N/A
Nearest person month worked: 1
Contribution to Project: No change

Name: Katie Schwartz
Project Role: Research Assistant
Researcher Identifier: N/A
Nearest person month worked: 2
Contribution to Project: Participant recruitment and assessment, data analysis

Changes in active other support of the PI since the last reporting period

Dr Kath Bogie (PI)

Studies ended 10/01/15 -09/30/16

None

New studies 09/30/15 -09/30/16

Started 10/01/15: APTC Garverick Innovation Incentive Program

PI: Majerus S, Cleveland VA Medical Center

Percent effort: 0.6 cal months (*Co-Investigator uncompensated*)

Wireless graft patency monitoring using PDMS-based flexible pulsation sensors

Started 12/01/15: NIH R56: National Institute of Dental and Craniofacial Research

PI: Kaigler D, University of Michigan

Percent effort: 1.2 cal month (*Co-Investigator*)

Customized craniofacial stem cell therapy for craniofacial bone defects

Other organizations involved as partners

Organization Name: Case Western Reserve University

Location of Organization: Cleveland, Ohio

Partner's contribution to the project: Collaboration & Facilities

8. Special Reporting Requirements

Not applicable

9. Appendices

Not applicable